BBT-059, A Promising Countermeasure for Multi-Organ Injury in mice exposed to both high and low LET radiation

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MHSRS Annual meeting, Kissimmee, FL, 3-6 Aug 2026

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Armed Forces Radiobiology Research Institute (AFRRI)

Mission Statement

To protect United States Armed Forces personnel against radiological threats through research, education, and training

DOD's Urgent Need for Radioprotectants/Prophylactics for H-ARS

- **There are no FDA-approved radioprotectants or prophylactics for Hematopoietic Acute Radiation Syndrome (H-ARS)**
- **Need is driven in part by current geopolitical events, e.g. Ukraine, South China Sea**
- **An FDA-approved radioprotectant/prophylactic may benefit military and civilian first-responders operating in a contaminated space**

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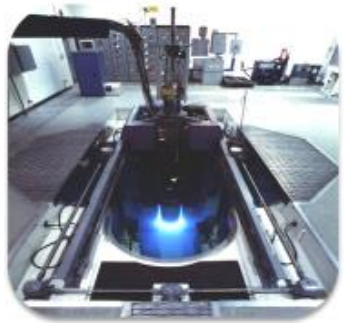
BBT-059 as a promising radioprotectant against H-ARS

BBT-059
24 or 12h Pre-TBI

Day 0

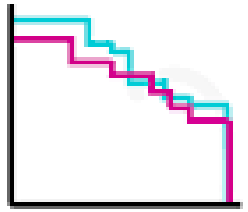
Low LET Co-60 (Gamma)



*65% neutron and 35% gamma

High LET TRIGA (Mixed field*)

30-days



KAPLAN-MEIER CURVE

0.3mg/kg
Single subcutaneous dose
C57BL/6 mice
Vehicle: formulation buffer (10mM sodium phosphate, 4% mannitol, 1% sucrose, pH 6.2)

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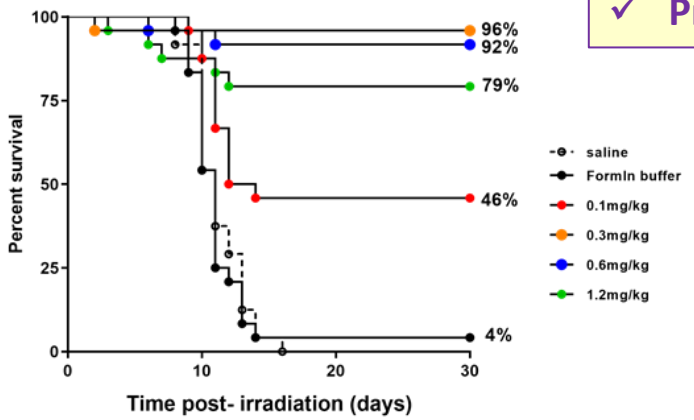
BBT-059: A promising countermeasure in mice exposed to low LET radiation

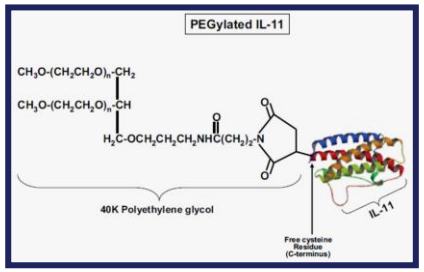
Single dose BBT-059, 24 h pre-TBI or 24 h post-TBI
Vehicle: formulation buffer (10mM sodium phosphate, 4% mannitol, 1% sucrose, pH 6.2)

Co-60

BBT Dose response Pre-TBI



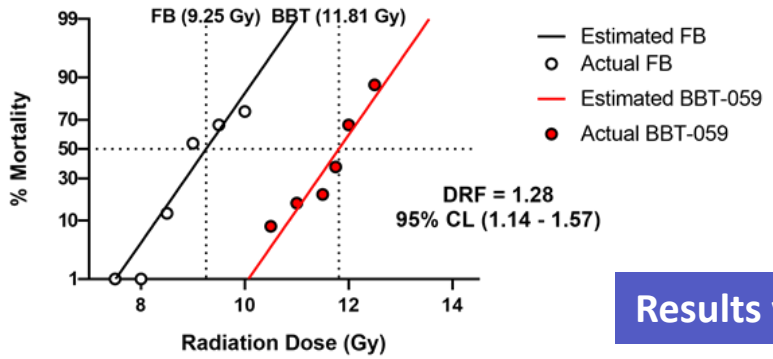
- ✓ Survival efficacy from -24 h to +24 h
- ✓ Optimal dose 0.3 mg/kg given once Subcutaneous
- ✓ Prophylactic Dose Reduction Factor = 1.28



Kumar, V. P., Biswas, S., Sharma, N. K., Stone, S., Fam, C. M., Cox, G. N., & Ghosh, S. P. (2018). *Health Phys, 115*(1), 65-76.

Sharma NK, Holmes-Hampton GP, Kumar VP, Biswas S, Wuddie K, Stone S, Aschenake Z, Wilkins WL, Fam CM, Cox GN, Ghosh SP. (2020). *Sci Rep.* 10(1):6825

DRF Pre-TBI



Recombinant human IL-11
- Increased Platelet Counts
- Required daily dosing
- Led to severe side effects

BBT-059 is a PEGylated IL-11
- (PEG-*179C) at C terminus
- Single dose in rats stimulated circulating platelet production for up to 10d

Results validated in female mice

n= 24- 25/group

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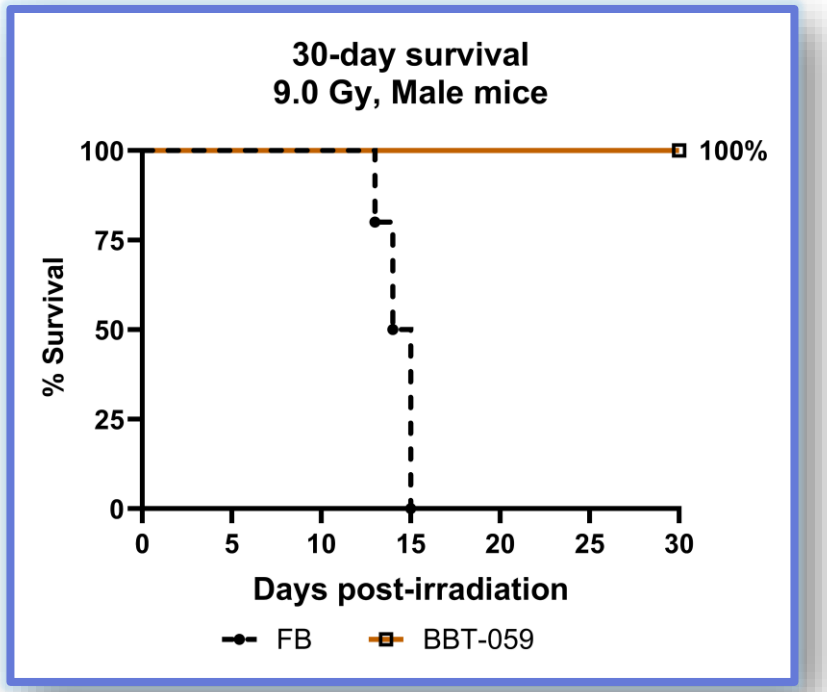
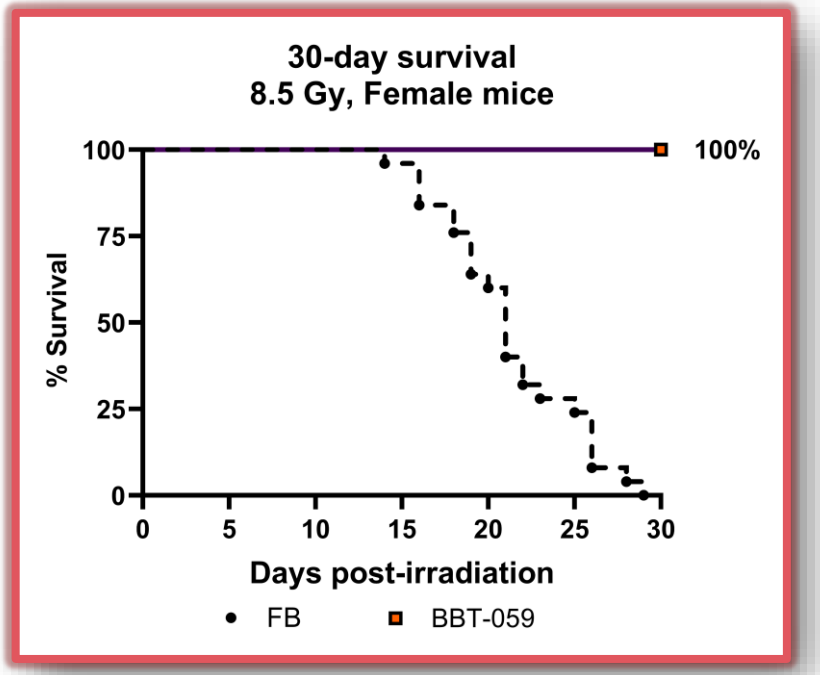
Pre-treatment with BBT-059 (-12 h) improved survival in low LET exposure (C57BL/6 mice)



Statistics	Significance
Log-rank test (Mantel Cox)	p≤ 0.0001
Fisher's exact test	p≤ 0.0001

Co-60 (Gamma)

LD100/30



Statistics	Significance
Log-rank test (Mantel Cox)	p≤ 0.0001
Fisher's exact test	p≤ 0.0001

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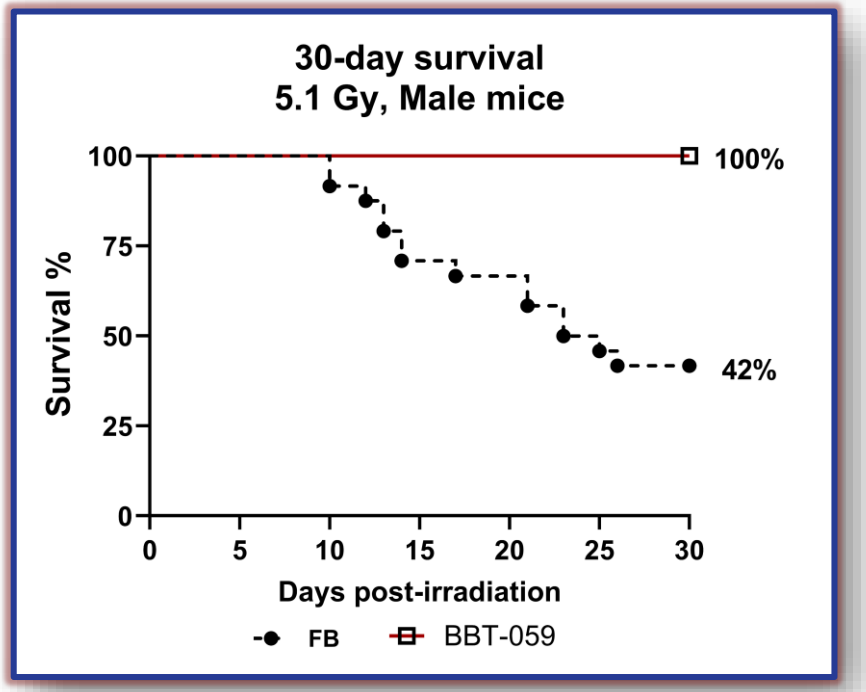
Pre-treatment with BBT-059 (-12 h) improved survival in high LET exposure (C57BL/6 mice)

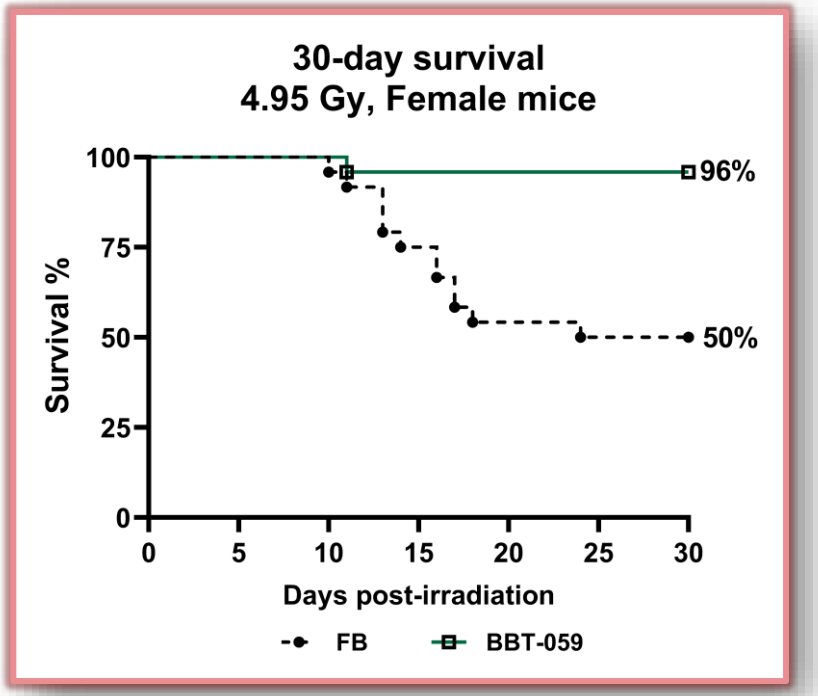


Statistics	Significance
Log-rank test (Mantel Cox)	p≤ 0.0001
Fisher's exact test	p≤ 0.0001

TRIGA (Mixed field*)

*65% neutron and 35% gamma

LD50/30



Statistics	Significance
Log-rank test (Mantel Cox)	p= 0.0005
Fisher's exact test	p= 0.0007

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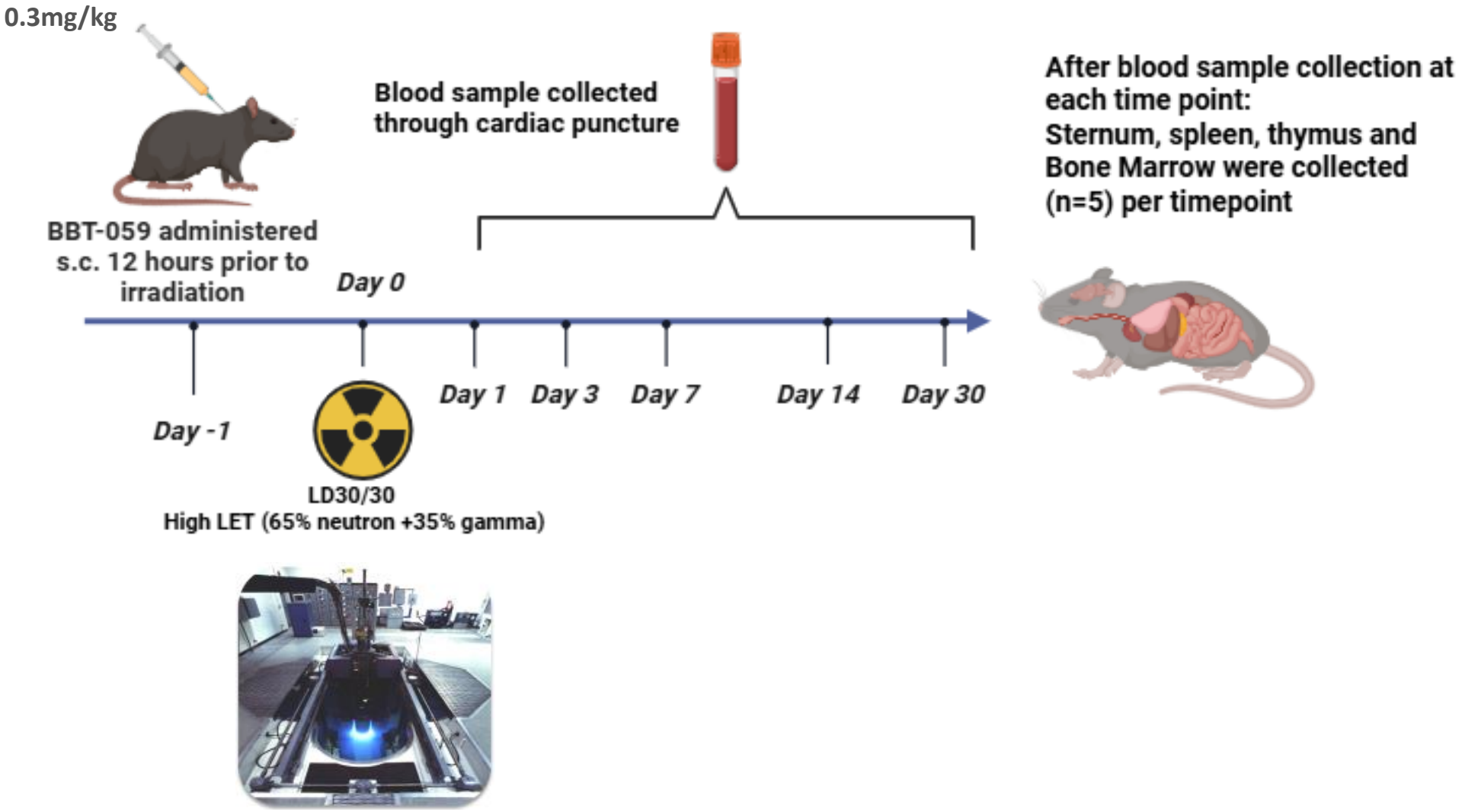
Hematopoietic recovery in H-ARS model of high LET (65% neutron and 35% gamma)



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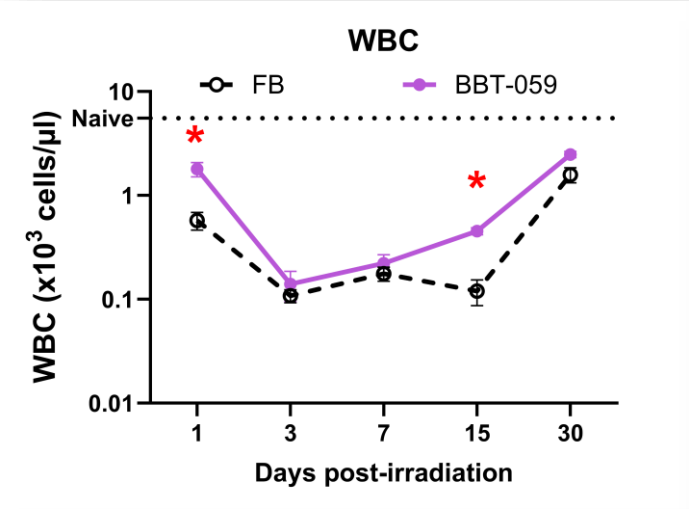
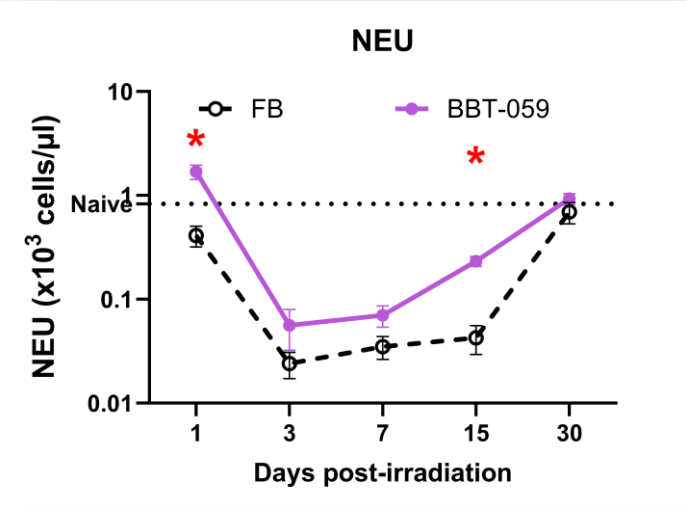
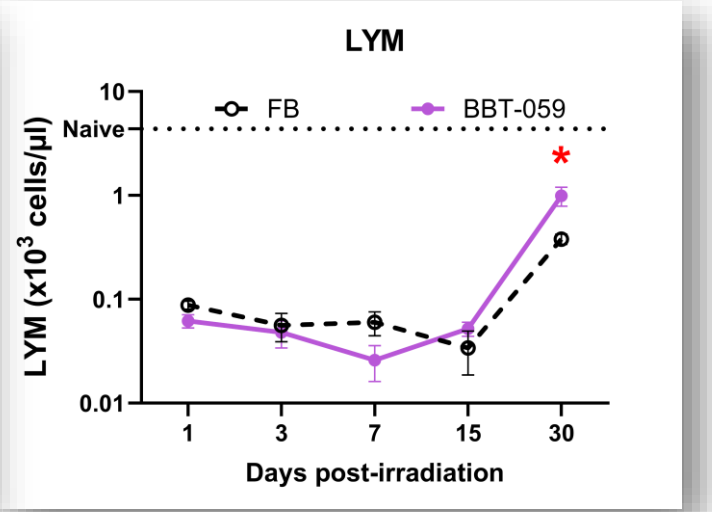
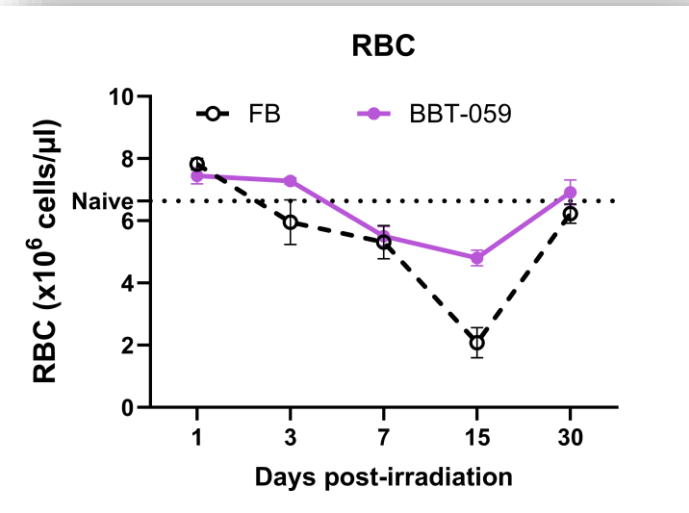
BBT-059 accelerated peripheral blood and bone marrow progenitor cells recovery from high LET exposure

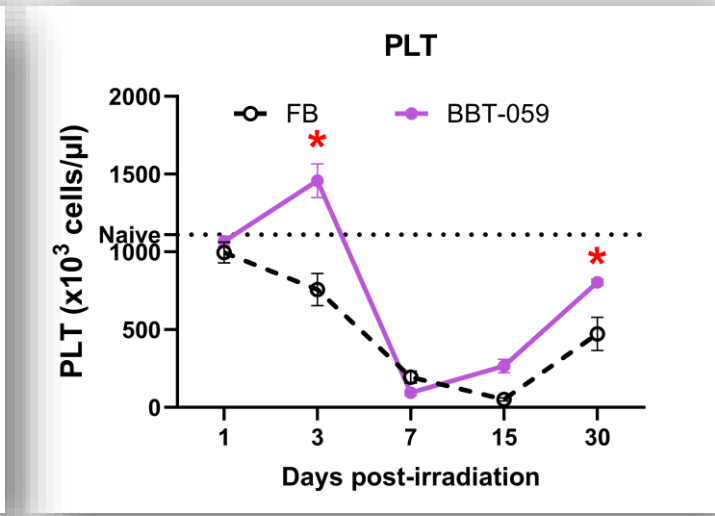


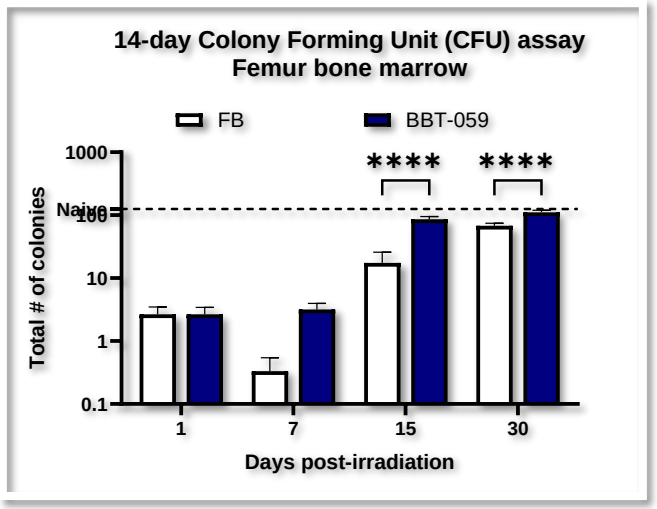




Male C57BL/6 mice
LD30/30 TBI @ 4.9 Gy







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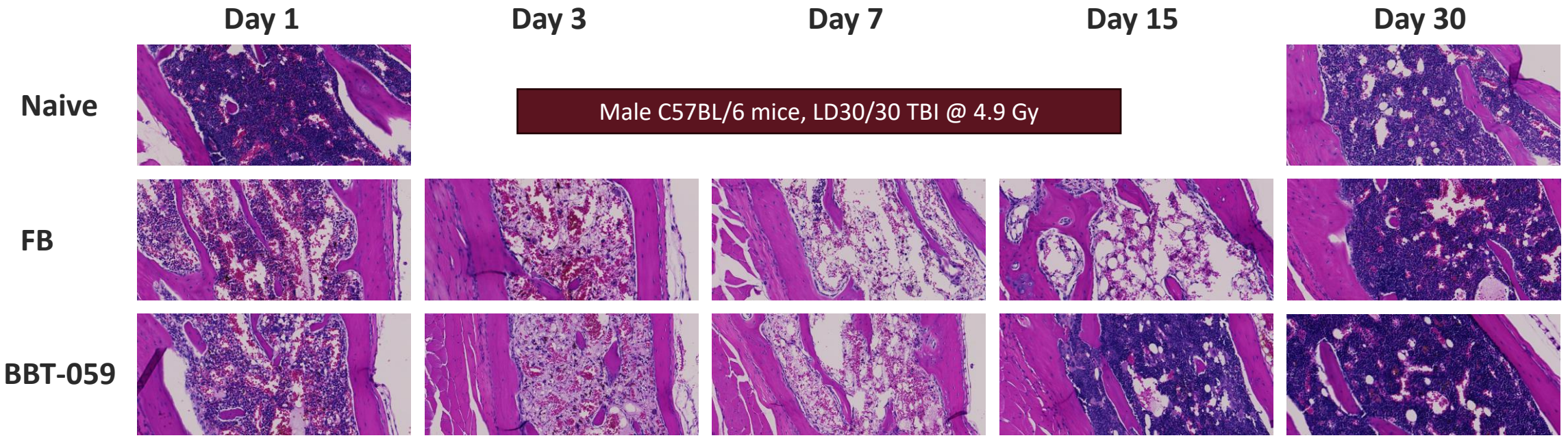
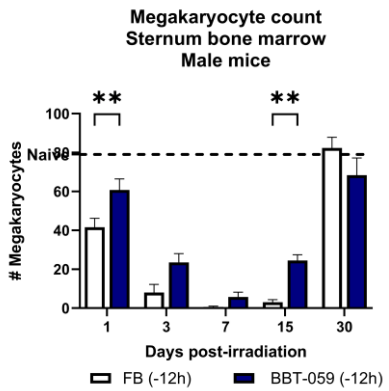
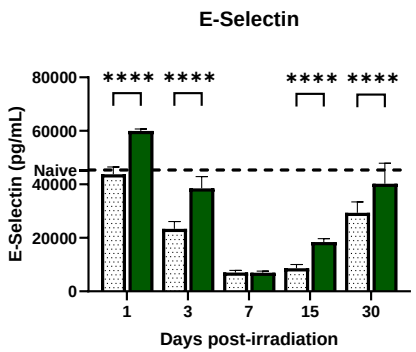
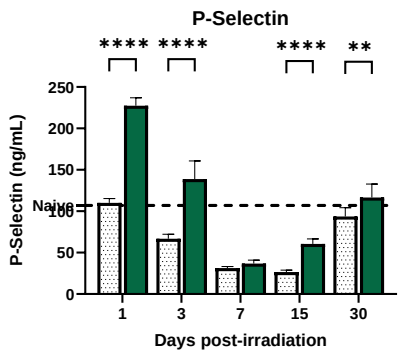
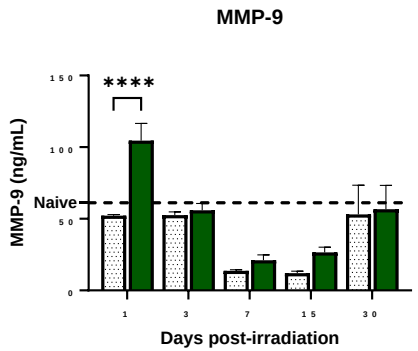
BBT-059 improves bone marrow cellularity, megakaryocytes and endothelial markers in mice exposed to high LET exposure











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BBT-059 Efficacy at 14 Gy Partial Body Exposure

LINAC (PBI)

RADIATION RESEARCH 201, 19–34 (2024)
0033-7587/24 $15.00

DOI: 10.1667/RADE-23-00068.1

Development of a Multi-Organ Radiation Injury Model with Precise Dosimetry with Focus on GI-ARS

Vidya P. Kumar,[1] Kefale Wuddie, Alena Tsioplaya, Alia Weaver, Gregory P. Holmes-Hampton, Sanchita P. Ghosh

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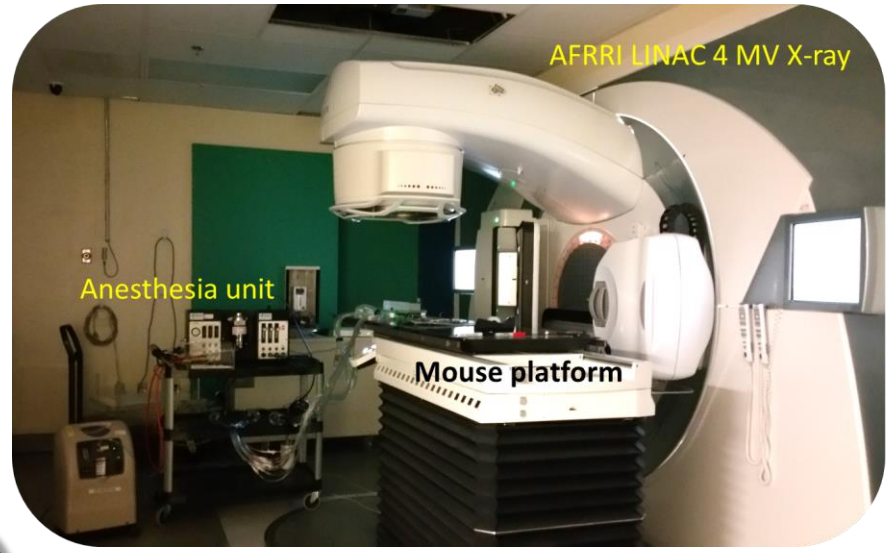
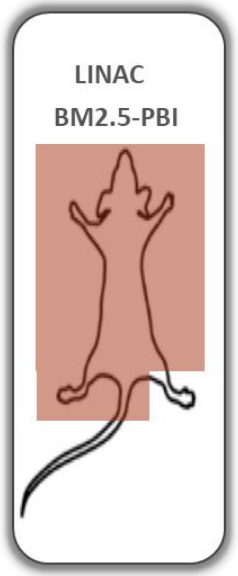
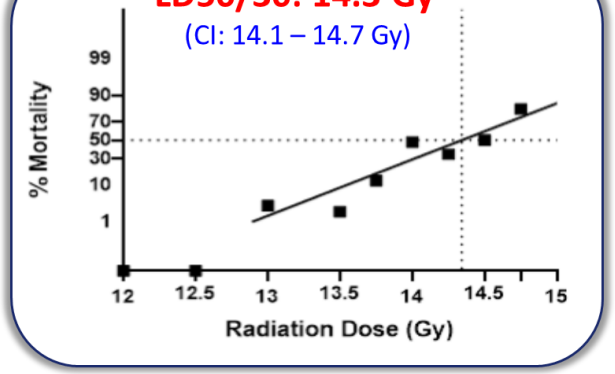
~2.5% bone marrow sparing (BM2.5)
(avoiding radiation to 1 hind limb & tail)





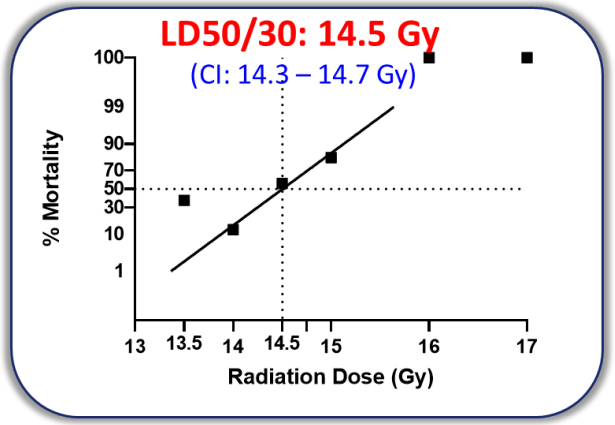
Males

LD50/30: 14.3 Gy
(CI: 14.1 – 14.7 Gy)



Females

LD50/30: 14.5 Gy
(CI: 14.3 – 14.7 Gy)



- **High energy X-rays** (4MV)
- **Higher throughput**
- Animals under anesthesia
- Amenable variable BM sparing

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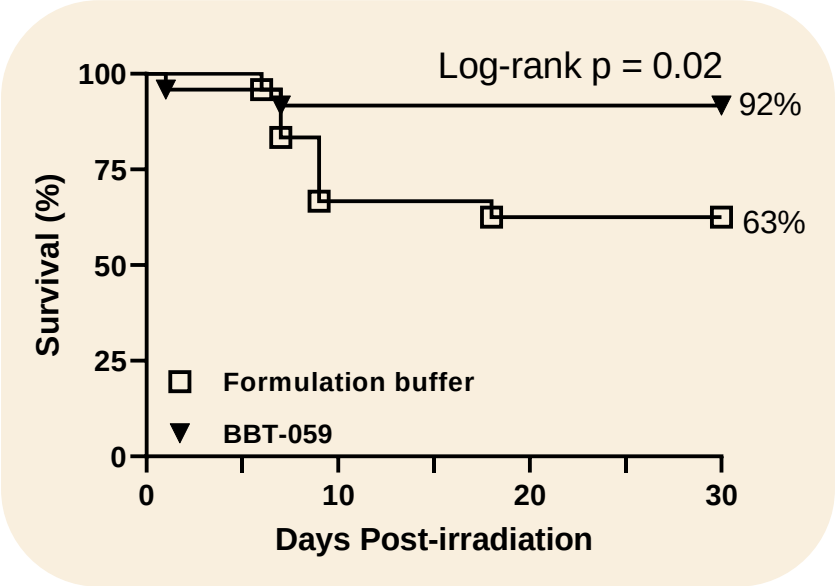
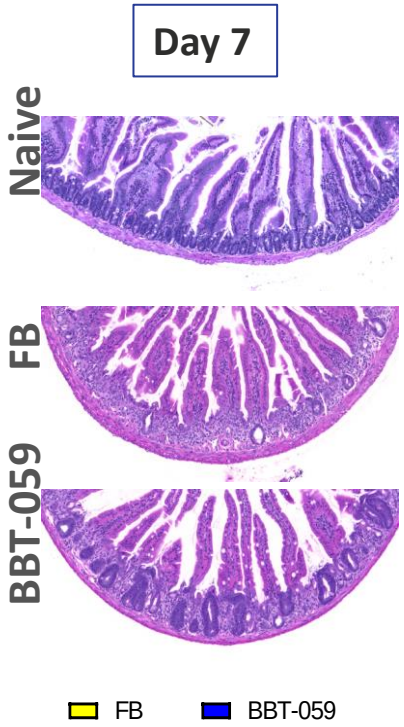
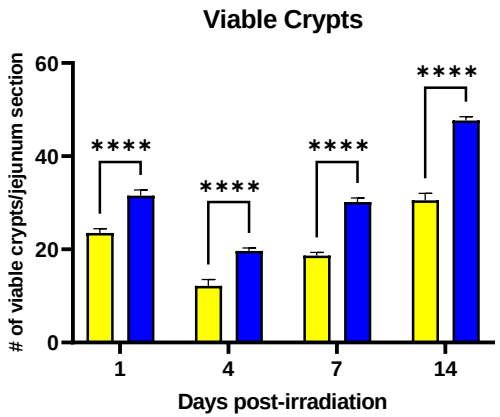
Survival Efficacy & GI Tissue Recovery at 14 Gy PBI with BBT-059

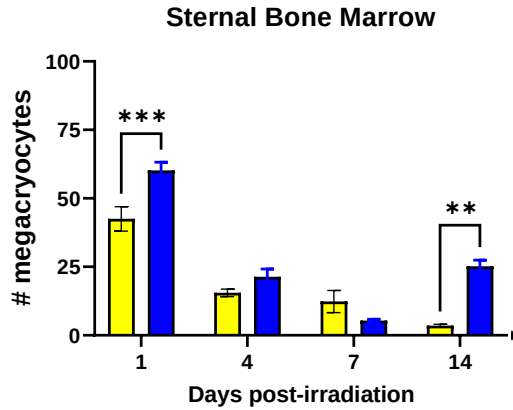
LINAC (PBI)

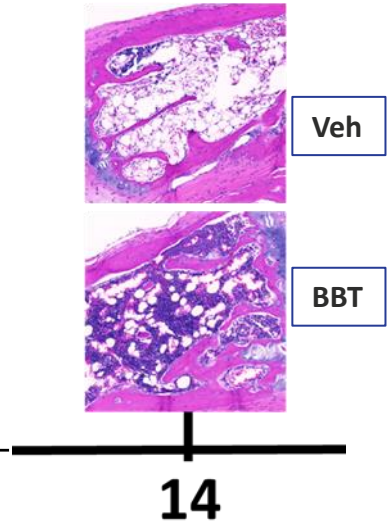
Time of Administration: 24 h pre-PBI











- ✓ Significant survival efficacy when exposed to 14 Gy-PBI
- ✓ Significant accelerated recovery of jejunal crypt counts in BBT grp
- ✓ Significant recovery of sternal bone marrow with BBT-059

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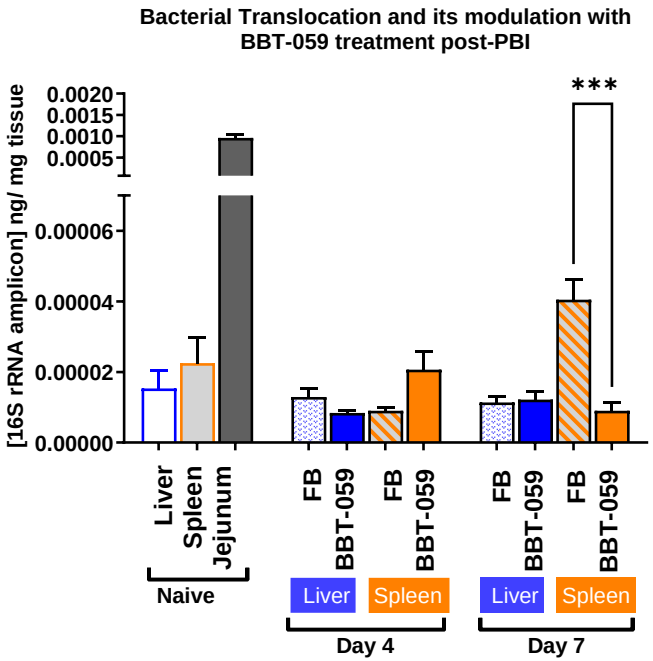
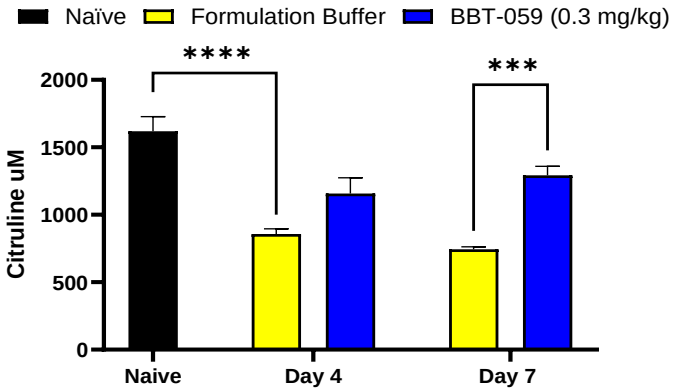
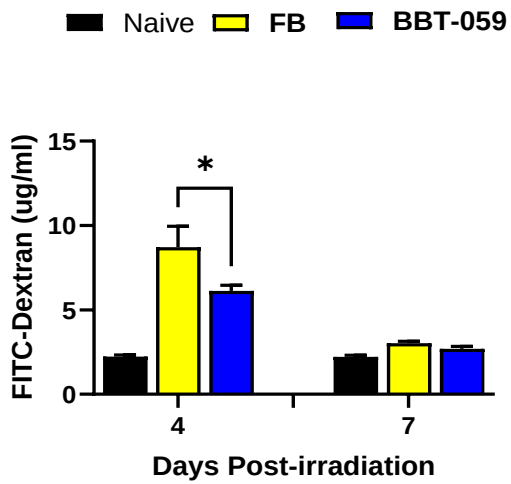
Reduced bacterial load, increased citrulline levels, and FITC-Dextran with BBT-059 (-24 h)

LINAC (PBI)







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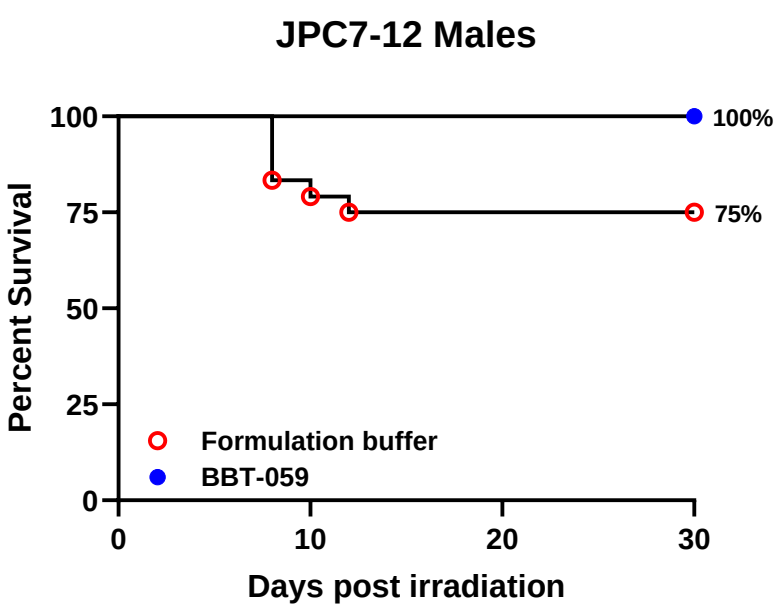
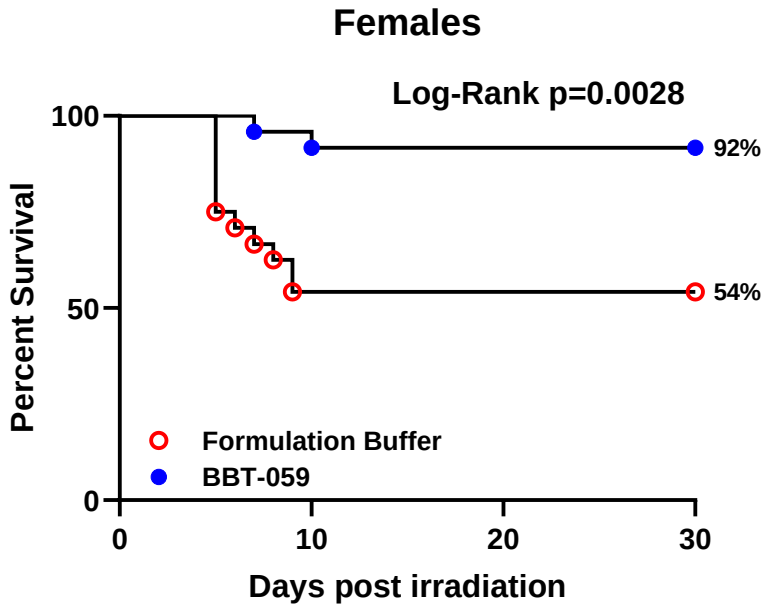
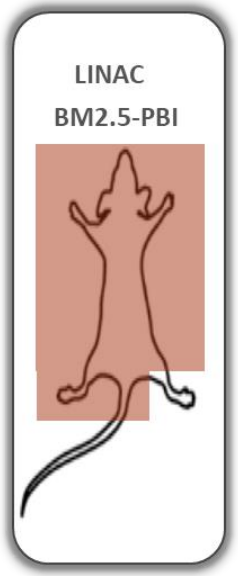
BBT-059 is effective rescuing mice from high dose of PBI administered 12 h pre-exposure (14.5 Gy)

LINAC (PBI)

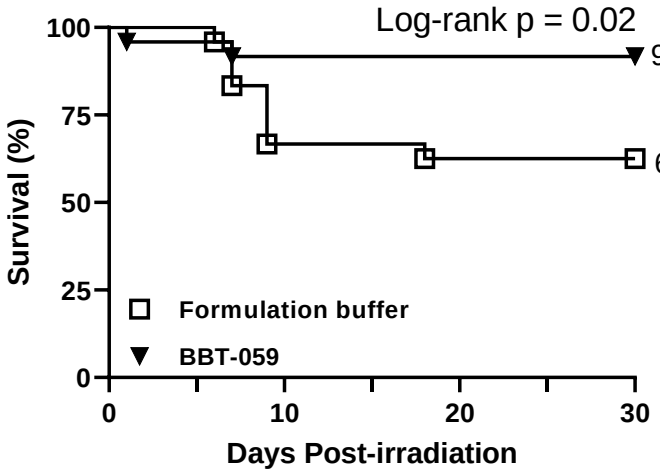
-12 h







-24 h



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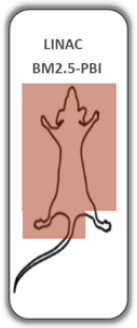
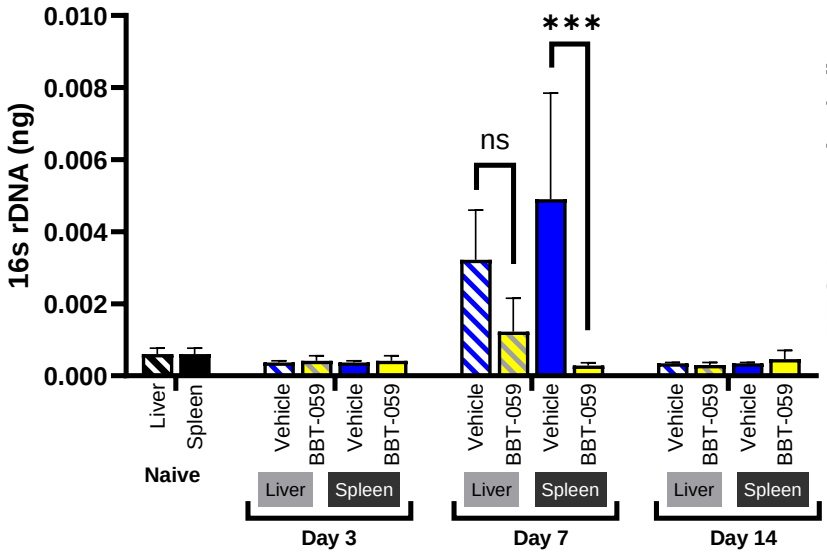
GI Recovery (males) with BBT-059: 12 h pre-treatment (14 Gy)

LINAC (PBI)

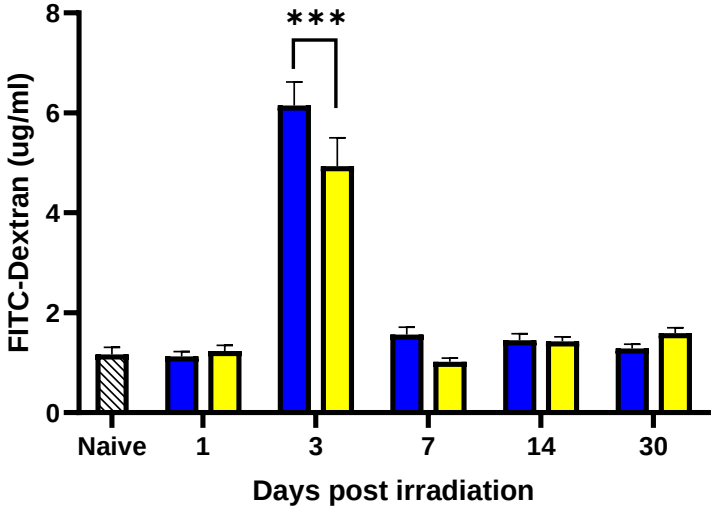
14 Gy BM2.5-PBI



Reduction in Bacterial Translocation

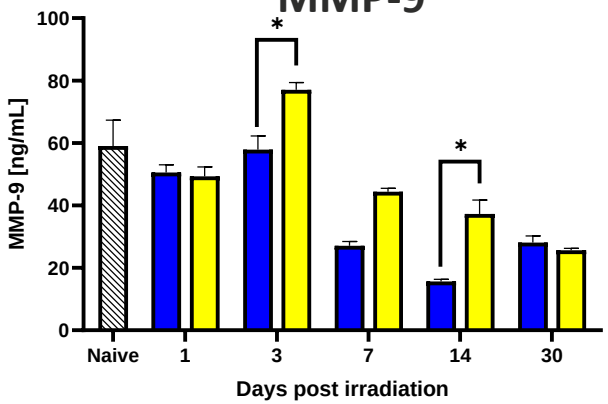


Recovery of gut barrier function

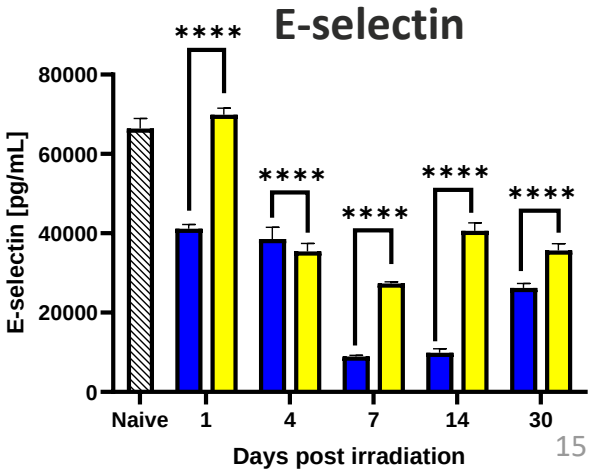


- ✓ GI protection shown by significantly lower bacterial load on the liver and spleen
- ✓ And in gut-barrier function test
- ✓ Recovery of endothelial markers and GI-ARS biomarker citrulline in BBT group.

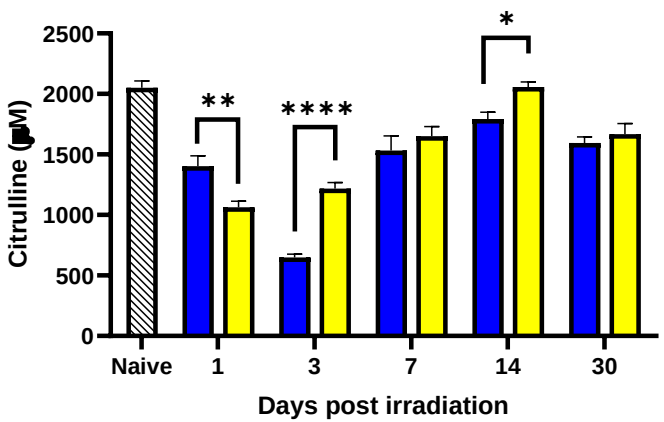
MMP-9



E-selectin



Citrulline



Vehicle

BBT-059

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METABOLOMIC ANALYSIS IN JEJUNUM AND FECAL MATTERS (MALES)

Study Design Overview & Objective

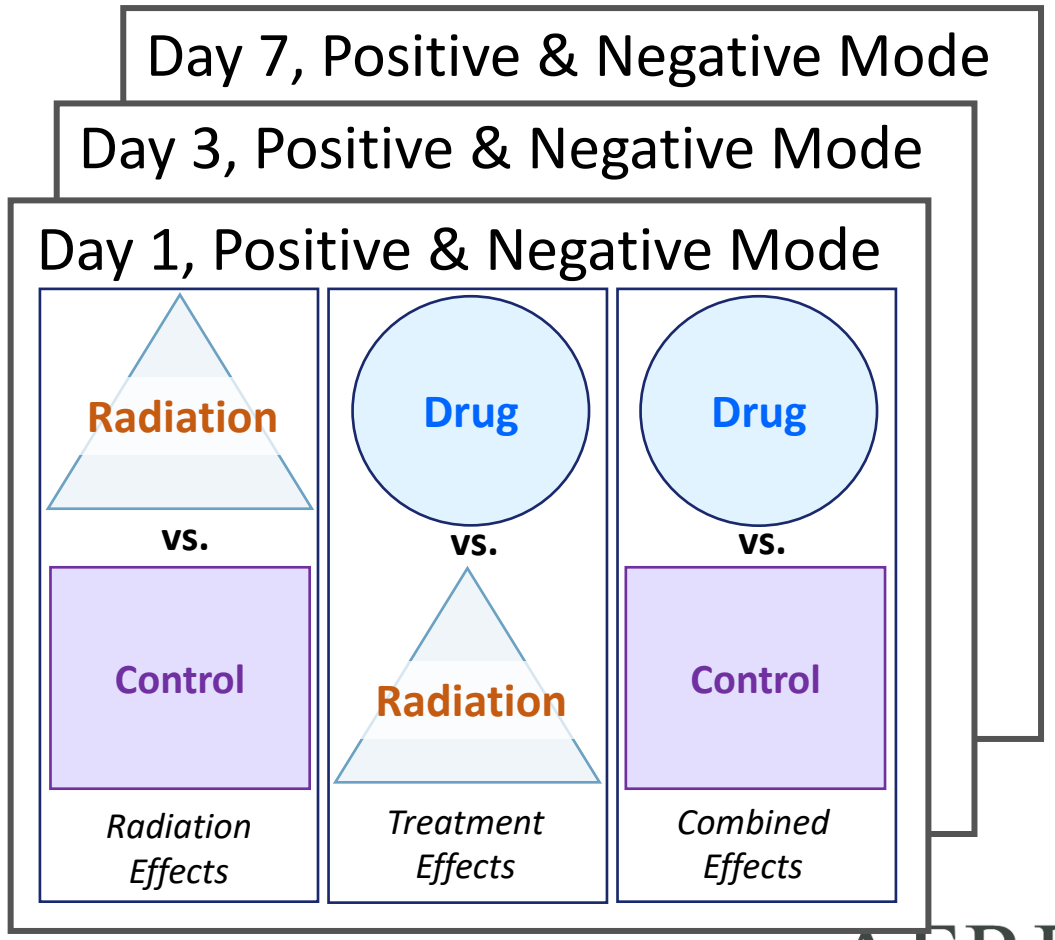
Objective: To analyze the fecal and jejunal metabolomic effect of drug (BBT-059) compared to irradiated (radiation) or control (naïve) treated mice.

LINAC (PBI)

Study design overview: treatment groups & time points

T_x	Radiation	Drug	Time (Days)
Radiation (n = 4)	X		1, 3, 7
Drug (n = 4)	X	X	1, 3, 7
Control (n = 4)			1

Baseline



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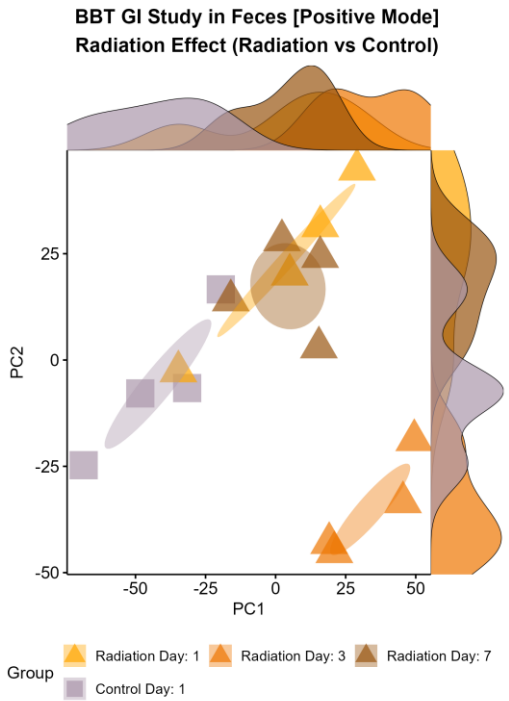
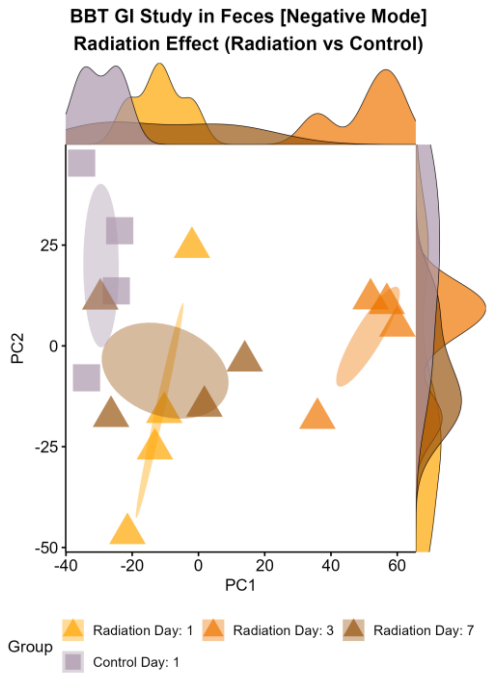
Fecal Metabolomics Results

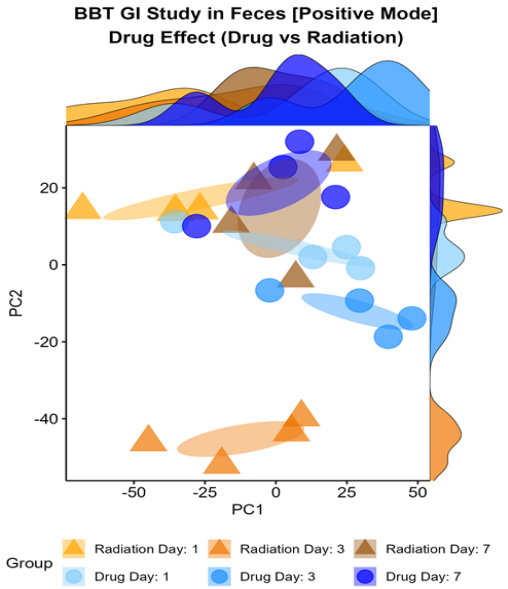
Radiation Effect (Radiation vs. Control)

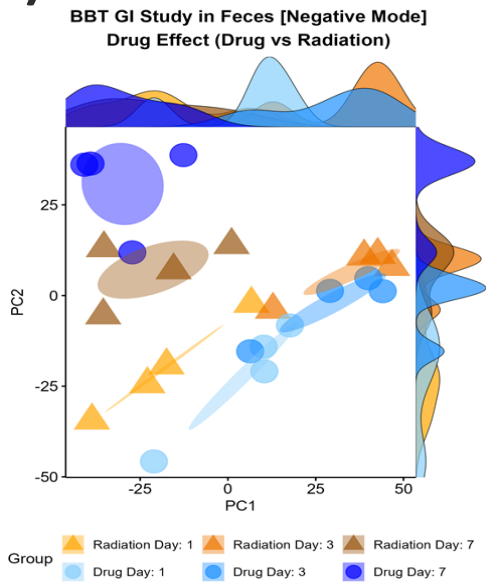




- Radiation days 1 and 7 cluster together
- Control shows modest separation from radiation groups along PC1
- Day 3 separates out most from the control, suggesting a peak of metabolomic dysregulation

Drug Effect (Radiation + Drug vs. Radiation)





- ESI+
  - Drug and radiation groups largely overlap at days 1 and 7
  - Day 3 radiation separates from other groups, while day 3 drug group is closer to days 1 and 7, suggesting an ameliorative effect
- ESI-
  - Drug and groups separate from radiation groups at each timepoint along PC2
  - Day 3 ameliorative effect seen in ESI+ not present in ESI- mode

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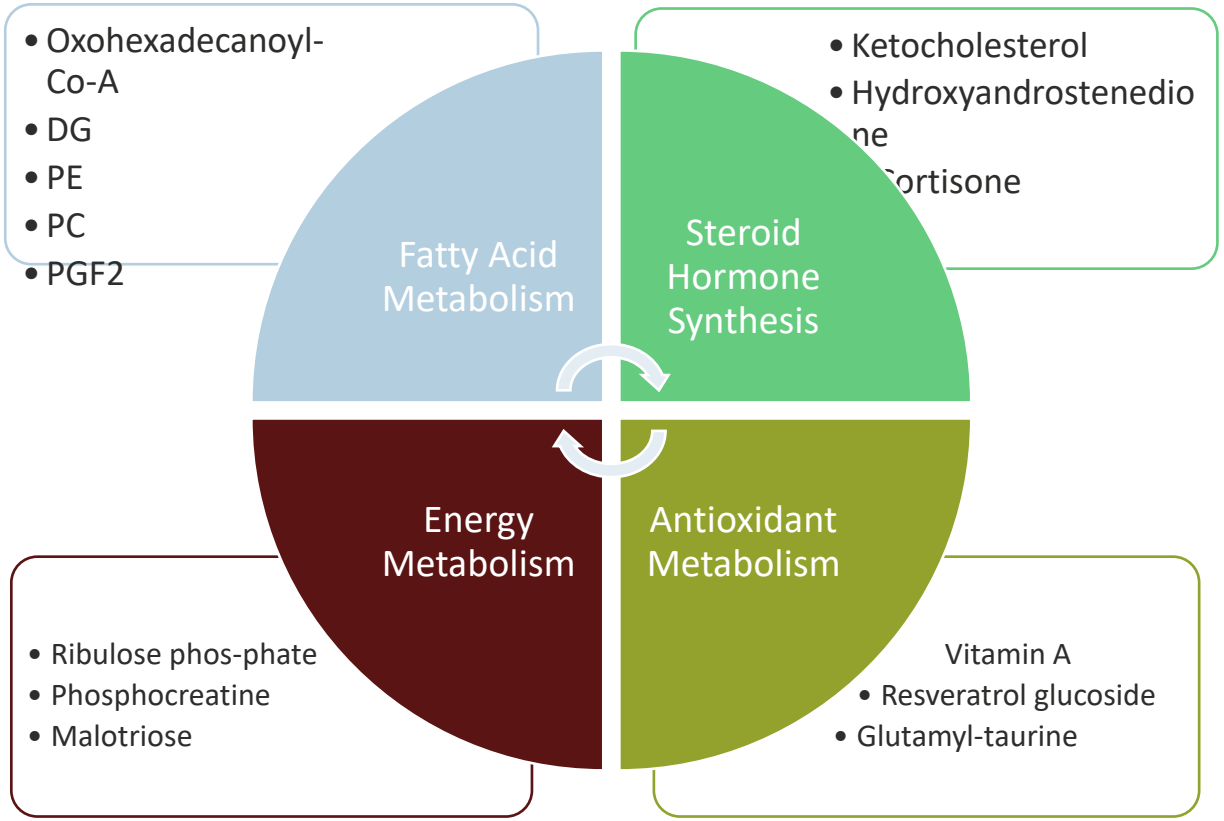
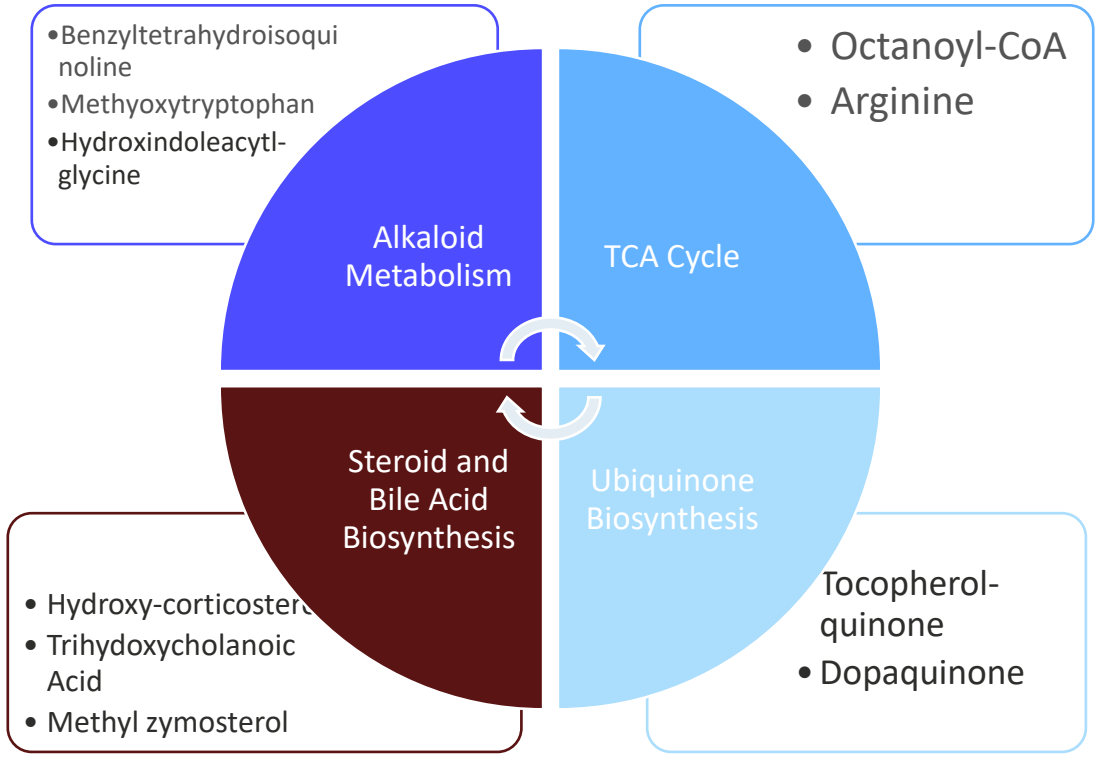
Radiation Effect: Top Analytes



Drug Effect: Top Analytes



Top pathways also included Fatty Acid metabolism, steroid hormone synthesis, energy metabolism, and antioxidant metabolism as in previous comparison

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Key Findings:

•**Peak Dysregulation:**

- Both fecal and jejunum metabolomes show peak disruption **3 days post-radiation**
- **Partial recovery** toward baseline by **Day 7** regardless of drug treatment

•**Drug Impact (BBT-059):**

- Reduces metabolic dysregulation, especially at **Day 3**

Jejunum: Overall metabolic effects are limited at early timepoints (**Day 1 and 3**)

- **Feces:** Some metabolic pathways remain perturbed despite treatment

•**Pathways Affected:**

- **Shared:** Antioxidants, fatty acids, steroid metabolism
- **Feces-specific:** TCA cycle, bile acid biosynthesis, and ubiquinone enriched in drug group

Summary of BBT-059 as an Efficacious MCM

- BBT-059, a long-acting PEGylated IL-11 analog, stimulates platelets, red blood cells and accelerated multilineage hematopoietic recovery.
- **Radioprotector** as well as **mitigator** in rodent models against **gamma, neutron and x-rays**
- Protects mice from both **hematopoietic** and **gastrointestinal injury**
- **BBT-059 is a promising countermeasure for H-ARS and GI-ARS**

Questions?

Thank you